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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/690,771 | 10/22/2003 | William Aloysius Nugent | 10010 (NP) | 6957 |

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EXAMINER

WITHERSPOON, SIKARL A

| | |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

1621

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/690,771

Applicant(s)

NUGENT ET AL.

Examiner

Sikarl A. Witherspoon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>2</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kronenthal et al (US 6,399,793).

Applicants claim a process for preparing alpha-chloroketones of formula (I) by reacting an alkyl ester of formula (II) with a sulfoxonium ylide of formula (III) to produce a keto sulfoxonium ylide of formula (IV), and then treating said keto sulfoxonium ylide with anhydrous HCl. Further limitations include the step of forming the sulfoxonium ylide of formula (III) by the reaction of a sulfoxonium salt with a base; the sulfoxonium salt being a trialkyl-sulfoxonium halide and the base being potassium tert-butoxide or potassium tert-amylate; the reaction of the keto sulfoxonium ylide of formula (IV) with anhydrous HCl being carried out in an organic solvent at a temperature in the range of 60 to 80° C; the solvent being selected from dimethylformamide, tetrahydrofuran, acetonitrile, or toluene; the HCl being generated in situ by reacting a source of chloride and an organic acid; the source of chloride being lithium chloride, and the organic acid being methanesulfonic acid.

Kronenthal et al teach a process for preparing alpha-chloroketones wherein an aryl ester is treated with a sulfur ylide to produce an intermediate keto ylide, which is

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subsequently treated with a source of chloride, preferably lithium chloride, and an organic acid, such as methanesulfonic acid, to produce the alpha-chloroketone. The sulfur ylide is prepared from a sulfoxonium salt by reaction with a suitable base in an organic solvent. Suitable sulfoxonium compounds include trialkyl sulfoxonium halides, and preferable bases include sodium hydride, potassium tert-butoxide, and potassium tert-amylate. The reaction is carried out in an organic solvent at a temperature in the range of 60 to 80° C. Upon formation of the sulfur ylide compound, it is reacted with the aryl ester starting material to form the keto ylide intermediate, said intermediate subsequently being converted to the alpha-chloroketone by reaction with a source of chloride in an organic solvent such as tetrahydrofuran, toluene, or acetonitrile, at an initial temperature of 0 to 5° C, up to a temperature of about 65° C (see col. 3, line 9 to col. 4, line 17).

The process taught by Kronenthal et al differs from the instant process in that a different starting material is employed; hence, a different intermediate keto ylide and subsequent alpha-chloroketone are formed. Specifically, the starting material used in the process of Kronenthal et al is an *amino*-substituted *aryl* ester, while applicants use an *alkyl* ester that has substitution other than by an amino group (see definitions of the R-group in claim 1). Also, Kronenthal et al do not *expressly* teach that anhydrous HCl is used to react with the keto sulfoxonium ylide to form the alpha-chloroketone.

The examiner purports that the present invention would have been obvious to a person of ordinary skill in the art for two reasons. First, with regard to the use of an aryl ester starting compound versus an alkyl ester starting compound, the examiner purports

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that a person of ordinary skill in the art would recognize that the actual group that is attached to the carboxylic moiety of the starting compound, i.e., an alkyl group or an aryl group, is immaterial, because in such a reaction wherein there is a homologation of an ester compound to a keto sulfoxonium ylide, a sulfur ylide (or sulfoxonium ylide) is going to react with the ester at the carboxylic site. In other words, the substituent attached to the carboxylic moiety will be cleaved by and replaced with the sulfur ylide so as to produce the corresponding keto ylide (or keto sulfoxonium ylide). Accordingly, the use of an aryl-ester in the process taught by Kronenthal et al renders the use of an alkyl-ester in applicants' process, obvious.

With regard to the use of an amino-substituted ester versus an ester not having an amino substitution, the examiner asserts that it would have been obvious to a person of ordinary skill in the art, at the time the present invention was made, to modify the substitution of the ester starting compound taught by Kronenthal et al to include substitution other than by an amino group. This is due to the fact that a person of ordinary skill would have recognized that the reactivity, or the site of reaction of the starting compound, is at the ester moiety. The substituents attached outside of the ester moiety are considered spectator molecules, i.e., they do not take place in the reaction. Accordingly, a person of ordinary skill in the art would have been motivated to modify the substitution of the starting compound taught by Kronenthal et al by the reasonable expectation of producing the desired, correspondingly substituted keto sulfoxonium ylide upon reaction of the ester starting compound with a sulfur ylide, as described by Kronenthal et al.

The examiner further contends that the fact that Kronenthal et al do not *expressly* mention anhydrous HCl in the reaction with the keto sulfoxonium ylide is immaterial. The examiner's contention is predicated on the fact that the reference clearly teaches that "the keto ylide compound is converted to the subject alpha-N-acyl-alpha-chloroketones by reaction with a source of chloride...most preferably lithium chloride, and an organic acid, for example methanesulfonic acid (col. 4, lines 7-11). It would have been apparent to a person of ordinary skill in the art that during the course of such a reaction, i.e., that of lithium chloride and an organic acid such as methanesulfonic acid, HCl would be liberated, and said HCl could be used, in effect, as a further source of chloride.

Claims 20-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kronenthal et al (US 6,399,793).

The instant claims are drawn to a process for preparing alpha-chloroketones of formula (Ia) by reacting a methyl ester of formula (IIa) with a sulfoxonium ylide of formula (III) to produce a keto sulfoxonium ylide of formula (IVa), and then treating the keto sulfoxonium ylide with anhydrous HCl. Further limitations include the step of forming the sulfoxonium ylide of formula (III) by the reaction of a sulfoxonium salt with a base; the sulfoxonium salt being a trialkyl-sulfoxonium halide and the base being potassium tert-butoxide or potassium tert-amylate; the reaction of the keto sulfoxonium ylide of formula (IV) with anhydrous HCl being carried out in an organic solvent at a temperature in the range of 60 to 80° C; the solvent being selected from

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dimethylformamide, tetrahydrofuran, acetonitrile, or toluene; the HCl being generated in situ by reacting a source of chloride and an organic acid; the source of chloride being lithium chloride, and the organic acid being methanesulfonic acid.

Kronenthal et al teach a process for preparing alpha-chloroketones wherein an aryl ester is treated with a sulfur ylide to produce an intermediate keto ylide, which is subsequently treated with a source of chloride, preferably lithium chloride, and an organic acid, such as methanesulfonic acid, to produce the alpha-chloroketone. The amino group on the aryl ester may be protected by any art-recognized amino protecting group, such as t-butoxycarbonyl (BOC) or benzyloxycarbonyl (col. 3, lines 1-8). The sulfur ylide is prepared from a sulfoxonium salt by reaction with a suitable base in an organic solvent. Suitable sulfoxonium compounds include trialkyl sulfoxonium halides, and preferable bases include sodium hydride, potassium tert-butoxide, and potassium tert-amylate. The reaction is carried out in an organic solvent at a temperature in the range of 60 to 80° C. Upon formation of the sulfur ylide compound, it is reacted with the aryl ester starting material to form the keto ylide intermediate, said intermediate subsequently being converted to the alpha-chloroketone by reaction with a source of chloride in an organic solvent such as tetrahydrofuran, toluene, or acetonitrile, at an initial temperature of 0 to 5° C, up to a temperature of about 65° C (see col. 3, line 9 to col. 4, line 17).

The process taught by Kronenthal et al differs from the instant process in that a different starting material is employed. Specifically, the starting material used in the process of Kronenthal et al is an amino-substituted *aryl* ester, while applicants use an

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amino-substituted *alkyl* ester. Also, Kronenthal et al do not *expressly* teach that anhydrous HCl is used to react with the keto sulfoxonium ylide to form the alpha-chloroketone.

The examiner purports that the present invention would have been obvious to a person of ordinary skill in the art. First, with regard to the use of an aryl ester starting compound versus an alkyl ester starting compound, the examiner purports that a person of ordinary skill in the art would recognize that the actual group that is attached to the carboxylic moiety of the starting compound, i.e., an alkyl group or an aryl group, is immaterial, because in such a reaction wherein there is a homologation of an ester compound to a keto sulfoxonium ylide, a sulfur ylide (or sulfoxonium ylide) is going to react with the ester at the carboxylic site. In other words, the substituent attached to the carboxylic moiety will be cleaved by and replaced with the sulfur ylide so as to produce the corresponding keto ylide (or keto sulfoxonium ylide). Accordingly, the use of an aryl-ester in the process taught by Kronenthal et al renders the use of an alkyl-ester in applicants' process, obvious.

The fact that Kronenthal et al do not *expressly* mention anhydrous HCl in the reaction with the keto sulfoxonium ylide is immaterial. The examiner's contention is predicated on the fact that the reference clearly teaches that "the keto ylide compound is converted to the subject alpha-N-acyl-alpha-chloroketones by reaction with a source of chloride...most preferably lithium chloride, and an organic acid, for example methanesulfonic acid (col. 4, lines 7-11). It would have been apparent to a person of ordinary skill in the art that during the course of such a reaction, i.e., that of lithium

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chloride and an organic acid such as methanesulfonic acid, HCl would be liberated, and said HCl could be used, in effect, as a further source of chloride. As such, the instant claims are rendered obvious in view of the teaching of Kronenthal et al.

Claims 36-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kronenthal et al (US 6,399,793).

The instant claims are drawn to a process for preparing a keto sulfoxonium ylide of formula (IV) by reacting an alkyl ester of formula (II) with a sulfoxonium ylide of formula (III). Further limitations include the step of forming the sulfoxonium ylide of formula (III) by the reaction of a sulfoxonium salt with a base; the sulfoxonium salt being a trialkyl-sulfoxonium halide and the base being potassium tert-butoxide or potassium tert-amylate.

Kronenthal et al teach a process for preparing a keto sulfoxonium ylide wherein an aryl ester is treated with a sulfur ylide (sulfoxonium ylide) to produce a keto ylide (keto sulfoxonium ylide). The sulfur ylide is prepared from a sulfoxonium salt by reaction with a suitable base in an organic solvent. Suitable sulfoxonium compounds include trialkyl sulfoxonium halides, and preferable bases include sodium hydride, potassium tert-butoxide, and potassium tert-amylate (col. 3, lines 9-60).

The process taught by Kronenthal et al differs from the instant process in that a different starting material is employed; hence, a different intermediate keto ylide is formed. Specifically, the starting material used in the process of Kronenthal et al is an *amino*-substituted *aryl* ester, while applicants use an *alkyl* ester that has substitution other than by an amino group (see definitions of the R-group in claim 36).

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The examiner purports that the present invention would have been obvious to a person of ordinary skill in the art for two reasons. First, with regard to the use of an aryl ester starting compound versus an alkyl ester starting compound, the examiner purports that a person of ordinary skill in the art would recognize that the actual group that is attached to the carboxylic moiety of the starting compound, i.e., an alkyl group or an aryl group, is immaterial, because in such a reaction wherein there is a homologation of an ester compound to a keto sulfoxonium ylide, a sulfur ylide (or sulfoxonium ylide) is going to react with the ester at the carboxylic site. In other words, the substituent attached to the carboxylic moiety will be cleaved by and replaced with the sulfur ylide so as to produce the corresponding keto ylide (or keto sulfoxonium ylide). Accordingly, the use of an aryl-ester in the process taught by Kronenthal et al renders the use of an alkyl-ester in applicants' process, obvious.

With regard to the use of an amino-substituted ester versus an ester not having an amino substitution, the examiner asserts that it would have been obvious to a person of ordinary skill in the art, at the time the present invention was made, to modify the substitution of the ester starting compound taught by Kronenthal et al to include substitution other than by an amino group. This is due to the fact that a person of ordinary skill would have recognized that the reactivity, or the site of reaction of the starting compound, is at the ester moiety. The substituents attached outside of the ester moiety are considered spectator molecules, i.e., they do not take place in the reaction. Accordingly, a person of ordinary skill in the art would have been motivated to modify the substitution of the starting compound taught by Kronenthal et al by the

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reasonable expectation of producing the desired, correspondingly substituted keto sulfoxonium ylide upon reaction of the ester starting compound with a sulfur ylide, as described by Kronenthal et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 recites the limitation "wherein said HCl is generated in situ..." in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim, since claim 36, to which the instant claim depends, does not make any mention of HCl. Claims 49 and 50 are dependent on claim 48 and thus have the same deficiency.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sikarl A. Witherspoon whose telephone number is 571-272-0649. The examiner can normally be reached on M-F 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sikarl A. Witherspoon 7/25/04

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